Review Article

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Anti-fatigue effect from *Ginseng Radix et Rhizoma*: a suggestive and promising treatment for long COVID

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Abstract

Two years after the coronavirus disease 2019 (COVID-19) outbreak, an increasing number of patients continue to suffer from long COVID (LC), persistent symptoms, and/or delayed or long-term complications beyond the initial 4 weeks from the onset of symptoms. Constant fatigue is one of the most common LC symptoms, leading to severely reduced quality of life among patients. *Ginseng Radix et Rhizoma*—known as the King of Herbs in traditional Chinese medicine—has shown clinical anti-fatigue effects. In this review, we summarize the underlying anti-fatigue mechanisms of *Ginseng Radix et Rhizoma* extracts and their bioactive compounds, with a special focus on anti-viral, immune remodeling, endocrine system regulation, and metabolism, suggesting that *Ginseng Radix et Rhizoma* is a potentially promising treatment for LC, especially regarding targeting fatigue.

Keywords: Fatigue, *Ginseng Radix et Rhizoma*, Long COVID, SARS-CoV-2

Graphical abstract: http://links.lww.com/AHM/A21.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally over the past 2 years. As an increasing number of people recover from SARS-CoV-2 infection, long COVID (LC) has become a growing concern[1–2]. Although there are no generally acknowledged case definitions or diagnostic criteria, LC is understood as persistent symptoms and/or delayed or long-term COVID-19 complications beyond 4 weeks from the onset of symptoms[3–5]. Most LC patients tested PCR-negative, indicating viral clearance. LC is the time lag between virus clearance and clinical recovery[6]. This time lag may last for weeks, or even months, after the onset of symptoms, when patients present with chronic and repeated fatigue[7–9]. In a pandemic which affects hundreds of millions of people worldwide, LC has posed a challenge for the healthcare system and economy for the years to come.

Compared with overtiredness, fatigue is a more profound state which leads to the constant weariness that impairs a person's vitality, determination, and concentration[10]. In LC, serious fatigue is one of the most reported and persistent symptoms, irrespective of the severity of the acute stage of COVID-19 and the levels of inflammatory markers[11]. Many cohort and cross-sectional studies have confirmed that fatigue is not only the most frequently reported symptom, but also the major manifestation of LC[12]. Therefore, studies regarding the mechanisms of fatigue in LC and effective treatment strategies are urgently required.

Known as the King of Herbs, *Ginseng Radix et Rhizoma* has a long history in traditional medicine. *Ginseng Radix et Rhizoma* is specifically referred to as the root and rhizome of the plant. Non-dried fresh *Ginseng Radix et Rhizoma* is rarely used in medical practice. According to traditional Chinese medicine, *Ginseng Radix et Rhizoma* has various effects, such as strengthening one's vitality, invigorating the spleen, replenishing one's *qi*, promoting fluid, and calming one's nerves. Modern pharmacology has revealed that *Ginseng Radix et Rhizoma* promotes virus clearance and is involved in bidirectional regulation of the immune, central nervous, and endocrine systems[13].

Ginseng Radix et Rhizoma has been used to treat both non-disease-specific and disease-induced fatigue[14], especially chronic fatigue syndrome[15], psychological stress[16], cancer[17–19] and menopause[20]. Both clinical practice and animal-based experiments have verified the various biological activities of *Ginseng Radix et Rhizoma*, such as anti-virus, anti-inflammation, the boosting of immune responses, and the reprogramming of one's metabolism[21]. All of these aspects can be attributed to LC-related fatigue. Based on CNKI and PubMed, we

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searched the literature of the last decade, briefly summarized the underlying anti-fatigue mechanisms of *Ginseng Radix et Rhizoma*, and discussed its possible applications to treat LC-related fatigue in this review.

Underlying mechanisms of anti-fatigue effects of *Ginseng Radix et Rhizoma*

Fatigue is a fundamental component of a diverse array of illnesses which affect a broad range of patients. The Institute of Medicine diagnostic criteria characterize myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) as a spectrum of five core symptoms: fatigue, sleep disturbance, cognitive changes, post-exertional malaise, and orthostatic intolerance[22]. In some cases, ME/CFS is thought to be triggered by infection, whereas in many other cases, no specific trigger can be identified. The pathogenesis of fatigue is poorly understood, and no specific diagnostic physical signs or biomarkers have yet been identified[23]. Disease-associated fatigue may be directly related to disease mechanisms (primary fatigue) or may be secondary to non-disease-specific factors. Although the pathophysiology and etiology of fatigue remain unclear, LC fatigue is characterized by various key features similar to ME/CFS[24]. For example, both types of fatigue have been suggested to be linked to chronic inflammation, over-activation of immune system, autonomic dysfunction, impaired functions in the hypothalamic-pituitary-adrenal axis, and neuroendocrine dysregulation.

Ginseng Radix et Rhizoma extracts have been reported to inhibit viral infections, maintain balanced immune responses, and restore impaired mitochondrial function (Figure 1A). Its anti-viral properties, in particular, is considered a feature of *Ginseng Radix et Rhizoma* and its extracts in viral-induced fatigue, which distinguishes it from other ME/CFS—such as postoperative, cancer, or other pathogen-related fatigue. Several studies have reported that oral administration of *Ginseng Radix et Rhizoma* extracts shows promising anti-viral effects (e.g., lowering viral loads and improving the viability of infected cells) against human immunodeficiency virus-1, influenza virus, rotavirus, and respiratory syncytial virus[25–26]. *Ginseng Radix et Rhizoma* can ameliorate chronic inflammation induced by a variety of autoimmune diseases—such as rheumatic diseases and inflammatory bowel disease—presumably by inhibiting the release of inflammatory cytokines, such as IL-6 and TNF-α[27–28]. In addition, a small-sized clinical study shows that administration of *Ginseng Radix et Rhizoma Rubra* extract reduced the production of inflammatory cytokines, such as TNF-α and IFN-γ, after chemotherapy[29]. Appropriate activation of adaptive immune cells (T and B cells) and stimulation of innate immune cells play a critical role in fighting infection. *Ginseng Radix et Rhizoma* has beneficial effects on the boosting functions of macrophages for the clearance of pathogens, dendritic cells for antigen presentation, B cells for antibody production, natural killer cells, and T cells for the more efficient removal of infected cells[12].

At the molecular level, *Ginseng Radix et Rhizoma* extracts exhibit direct or indirect modulatory effects on effector molecules involved in viral infection, cell viability and apoptosis, vesicular trafficking, and release (Figure 1B). A viral infection can activate PRR signaling, which stimulates IRF-family transcription factors that promote IFN expression with NF-κB and activates two signaling pathways induced by IFN-I and IFN-III. JAK1 and TYK2 kinases trigger the formation of the ISGF3 complex, which induces an anti-viral state in both signaling pathways[30]. Total ginsenosides may play an important role in the pathway of induction and anti-viral signaling of type I and type III IFNs by activating STAT1[31]. IL-6 is released in large quantities and binds to receptors to activate JAKs and stimulate STAT3 phosphorylation. STAT3 phosphorylates dimerization, transfers it to the cell nucleus, and regulates transcriptional activity[32]. It was found that the activity of JAKs could be suppressed by ginsenoside Rb1[13]. TRAF2, as an adapter

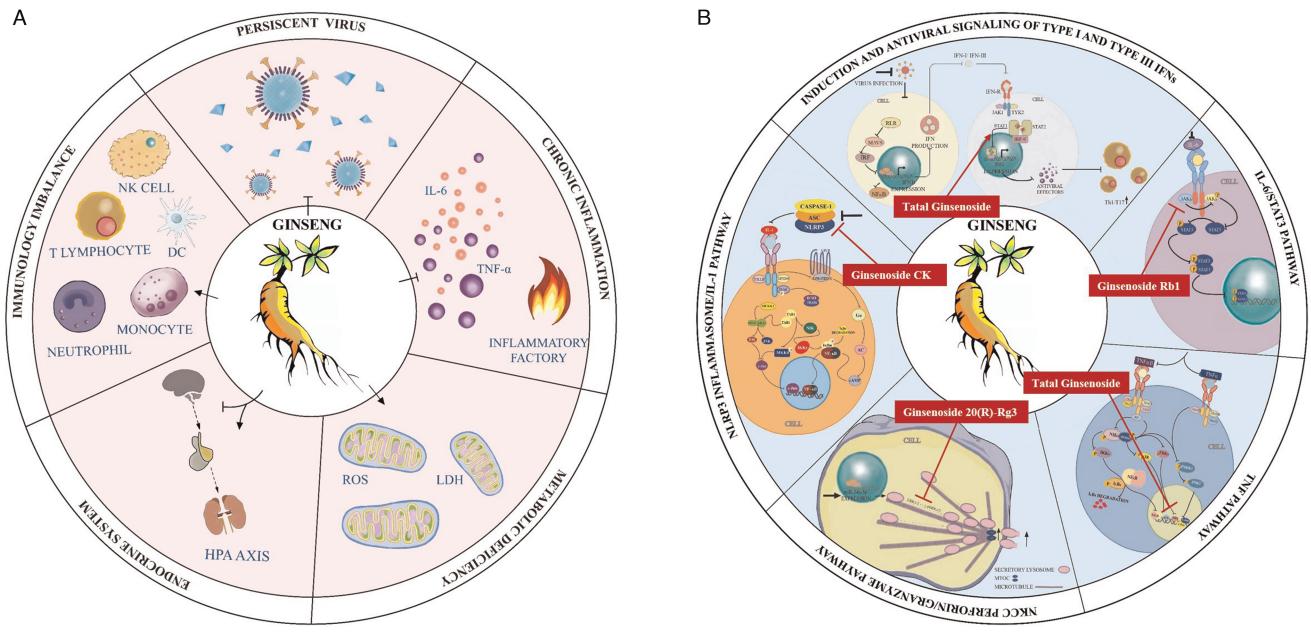

Figure 1. The potential mechanisms and signaling pathways of *Ginseng Radix et Rhizoma* to treat fatigue: (A) cellular function; (B) molecular pathways.

protein, activates the JNK and NF-κB signaling pathways to regulate immunocytes[33]. Total ginsenosides might down-regulate c-Jun gene expression resulting in the inhibition of the TNF pathway[31]. NLRP3 activation can stimulate superfluous inflammatory factors, leading to pyroptosis[34]. Ginsenoside CK could inhibit NLRP3-inflammasome activation to suppress IL-1 release to inhibit the overactive immune response[35]. In addition, miR-34a-5p down-regulation inhibits the ERK-mediated signaling pathway to decrease NKCC[36]. Ginsenoside 20 (R)-Rg3 promotes ERK1/2 phosphorylation to enhance NKCC of natural killer cells[37].

Active compounds from *Ginseng Radix et Rhizoma* with anti-fatigue effects

In *Ginseng Radix et Rhizoma*, various bioactive components have been identified—including ginsenoside, polysaccharides, and volatile oil[13,38–39]. To analyze the potential link between these bioactive components to anti-fatigue effects, we drew a word cloud using Excel to make use of word frequency counting and FineBI for analysis. Both *Ginseng Radix et Rhizoma* and fatigue were chosen as keywords. The word cloud indicates the active compounds of *Ginseng Radix et Rhizoma* and their major functions. A larger font size suggests a higher word frequency. The term "ginsenosides" is among the most frequently mentioned compounds (Figure 2). We focused on *Ginseng Radix et Rhizoma* extracts as well as its bioactive compounds and summarized their anti-viral effects and their ability to remodel immunity, promote anti-inflammation, regulate the endocrine system, and increase energy metabolism, all of which are linked to LC fatigue.

Anti-virus

Rare persistence of SARS-CoV-2 in the body may induce LC fatigue. The persistence of the virus can be due to persistent viremia in people with altered immunity and who have relapsed[40–41]. Clinical and animal studies have revealed the antiviral role of *Ginseng Radix et Rhizoma*. In HIV-infected patients, *Ginseng Radix et Rhizoma* not only induces genetic defects in the *nef* gene[42], but also shows its anti-HIV effect by preserving $CD4^+$ T cell counts, combined with zidovudine[43–45]. Diets containing *Ginseng Radix et Rhizoma* protect mice and ferrets from lethal infection with the H5N1 influenza virus[46], and ginsenosides even act as mucosal adjuvants against the influenza virus[47]. Ginsenosides Rb1, Rg1, and Rg3 inhibit the replication of the hepatitis A and B virus*es in vitro*[48–49]. Fermented *Ginseng Radix et Rhizoma* (black) suppresses the replication of SARS-CoV-2 and even lowers the number of viral RNA copies present in the extracellular environment[50]. Therefore, the antiviral properties of *Ginseng Radix et Rhizoma* shed light on its potential for clearing virus residue, which partially accounts for LC fatigue.

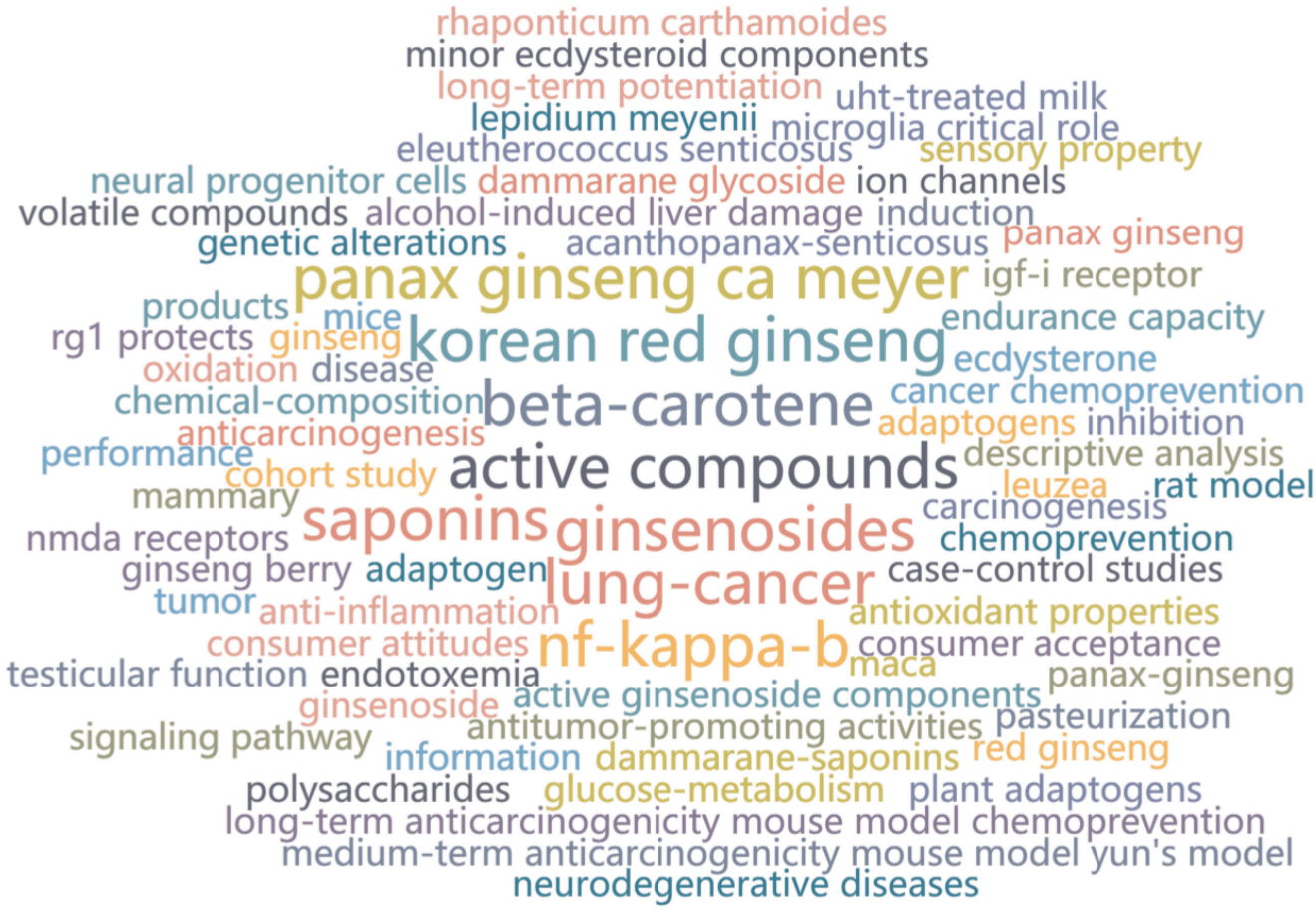

Figure 2. *Ginseng Radix et Rhizoma* active compounds and their main functions.

Immunity remodeling and anti-inflammation

The immune system responds to SARS-CoV-2 infection *via* both cellular and humoral responses. These responses are initiated by the innate immune system, which recognizes the virus and induces the production of proinflammatory cytokines and chemokines. It is followed by responses of the adaptive immune system, which consists of T cells that can directly kill virus-infected cells and B cells that produce pathogen-specific antibodies in the serum and mucosal surfaces[51]. In summary, two general anti-viral programs have been launched for patients with LC. The first is the engagement of cellular anti-viral defenses, which are mediated by the transcriptional induction of type I and III interferons (IFN-I and IFN-III) and the subsequent up-regulation of interferon-stimulated genes[30]. The second arm of the anti-viral response involves the recruitment and coordination of specific subsets of leukocytes, which are orchestrated primarily by cytokine and chemokine secretion[52].

SARS-CoV-2 triggers a several inflammatory mediators, thereby orchestrating an immune response that involves multiple cell types that are critical for viral clearance and the establishment of anti-viral immune memory. Failure to clear these infections can lead to excessive uncontrolled chronic inflammation in LC patients by evoking inflammatory programs. It is worth noting that patients with LC have highly activated innate immune cells, lacking naive T and B cells, and persistent cytokinemia[53], which indicates that immunity remodeling and anti-inflammation therapy may assist LC patients in overcoming fatigue. The bidirectional regulation of the immune system, coupled with the reduction of exuberant inflammatory cytokine production, paves the way for *Ginseng Radix et Rhizoma* to be a candidate for anti-LC fatigue (Figure 3).

Animal studies have confirmed the anti-fatigue role of *Ginseng Radix et Rhizoma* through regulation of the immune response and reduction of cytokine secretion. In chemotherapy-related fatigue mice model (with HT-29 subcutaneously injected into their right flanks), BST204 (a kind of purified dry extract from *Ginseng Radix et Rhizoma*) improves their performance in running wheel activity and forced swimming after treatment on the 27th day by 50% *via* raising the levels of muscle glycogen and declining the release of peripheral pro-inflammatory cytokines like TNF-α and IL-6[54]. In a weight-loaded swimming fatigue rat model, *Ginseng Radix et Rhizoma* down-regulated the protein expression of the pro-inflammatory cytokine IL-1β[55]. Ginsenosides, ginseng polysaccharides, and volatile oils are the major components for the relief of fatigue-induced symptoms. Based on the immune remodeling and anti-inflammatory mecha-

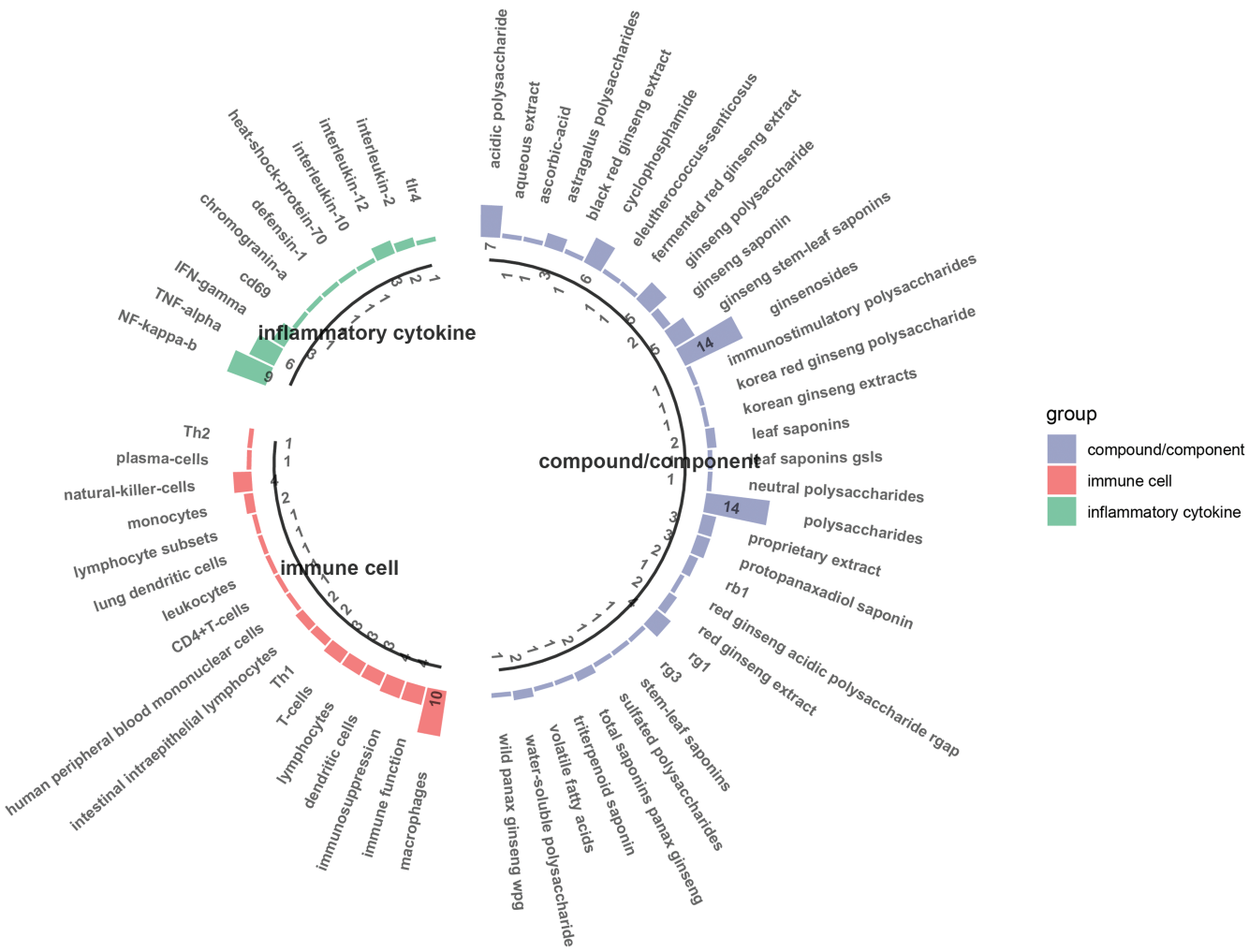

Figure 3. The active compounds of *Ginseng Radix et Rhizoma* associated with the immune system.

nisms, the anti-fatigue effects of the mixture extract and bioactive compounds in *Ginseng Radix et Rhizoma* are summarized in Table 1.

Regulation of the endocrine system

Fatigue in LC patients is closely related to hormonal dysregulation. Interestingly, compared with adults, LC symptoms are infrequently observed in children; conversely, women are more susceptible to LC-associated fatigue[11]. It has been reviewed in detail elsewhere that congestion of the glymphatic system and the subsequent toxic build-up within the central nervous system—caused by increased resistance to cerebrospinal fluid drainage through the cribriform plate as a result of olfactory neuron damage—may also contribute to LC fatigue[56]. A range of central, peripheral, and psychological hormones likely play a role in the development of LC fatigue.

Clinically, fermented *Ginseng Radix et Rhizoma* powder increases testosterone levels[57]. Ginsenoside Rg1 reverts the hypothalamic pituitary-adrenal axis to its normal function by improving the levels of serum cortisol (CORT) and testosterone[58]. Studies indicate that the water extract of *Ginseng Radix et Rhizoma* could protect cells from CORT-induced injury through

Table 1

Anti-fatigue effects of mixture extract from *Ginseng Radix et Rhizoma* by the immunity remodeling and anti-inflammation.

Categories	Natural products	Indicators	References
Saponins	Ginsenoside Rg6	TNF-α ↓, IL-10 ↑, miR-146a ↑	[77]
	Ginsenoside R3	$CD3^+T$ ↓, IL-4 ↓	[78]
		$CD8^+T$ ↑, IFN-γ ↑	
	Ginsenoside R1	TGF-β1↓, IL-1β ↓	[79]
	Ginseng total saponin (TGS)	NF-κB↓, COX-2 ↓	[80]
		Atg7 ↑, Beclin-1 ↑	
		LC3B I→LC3B II ↑	
	Ginsenoside CK	IL-4 ↑	[13]
		IL-6 ↓	
		IFN-γ ↑	[35]
		TNF-α ↓	
		TNF-α ↓, IL-6 ↓, IL-1β ↓	[81]
		IL-10 ↑	
		NF-κB ↓	[82]
	Ginsenoside Rg1 (G-Rg1)	TNF-α ↓, IL-6 ↓, NF-κB ↓	[83]
		Nrf2 ↑, HO-1 ↑	
		IL-1β ↓	[84]
		IL-1β ↓, IL-18 ↓, NLRP3 ↓	[85]
		IL-1β ↓, MMP-13 ↓, COX-2 ↓, PGE-2 ↓	[86]
	Ginsenoside Rb1	NF-κB ↓, MAPK ↓	[87]
		TNF-α ↓, IL-1β ↓, IκB ↓, IKK ↓	[88]
		TNF-α ↓, IL-6 ↓, IL-1β ↓	[89]
	Ginsenoside Rb3	IL-1β ↓, IL-6 ↓, IL-8 ↓	[90]
		IL-1β ↓, NLRP3 ↓	[91]
	Ginsenoside Rb2	IL-1β mRNA ↓, IL-6 mRNA ↓, TNF-α mRNA ↓	[92]
		TNF-α ↓, IL-6 ↓, iNOS ↓, COX-2 ↓, IKK/NF-κB ↓, MAPK ↓	[93]
	Ginsenoside Rd	IL-1β ↓, TNF-α↓, PGE2 ↓, NO ↓	[94]
	Ginsenoside Rc	IL-6 mRNA ↓, Bax ↓	[95]
		SIRT1 ↑, Bcl-2 ↑, procaspase-3 ↑	
	Ginsenoside Rh1	total inflammation cells ↓, eosinophils ↓, neutrophils ↓, lymphocytes ↓	[96]
	Ginsenoside Rf	IL-6 ↓, IL-1β↓	[97]
	Ginsenoside PPT, PPD, F1	IL-1β ↓	[98]
	Ginsenoside Rh2	TLR4 ↓, NF-κB p65 ↓, IL-6↓	[99]
	Ginsenoside Rk3	TNF-α ↓, IL-1β ↓, IL-6 ↓	[100]
	Ginsenoside PK1	TNF-α ↓, IL-1 ↓	[101]
	Ginsenoside Rg5	IL-1β ↓, IL-18 ↓, NF-κB ↓, Phosphorylation of p38 MAPK ↓	[102]
		iNOS ↓, TNF-α↓, IL-1β↓, COX-2 ↓, MMP-9 ↓	[103]
		TNF-α ↓, IL-1 ↓, COX-2 ↓, NF-kB ↓	[104]
Polysaccharides	Ginseng polysaccharide	NO ↓, TNF-α ↓, IL-6 ↓	[105]
		CD4+/CD8+T cell ↑	[106]
		IL-4 ↓, IL-17 ↓	
		NF-κB ↓, oxidative stress ↓, cytokine release ↓	[107]
Volatile oils	Ginseng volatile oil	MyD88 ↓, TLR4 ↓, TNF-α ↓, IL-6 ↓, IL-1β ↓	[108]

the interaction of GR-related functional proteins *in vitro*, such as heat-shock protein 90 and histone deacetylase 6 and the subsequent functional recovery of the endoplasmic reticulum and mitochondria[59]. It has been reported that ginsenoside Rg1 can protect neural stem cells and promote reproduction and committed differentiation of neural stem cells through anti-oxidation[60–64]. Ginsenoside-Rg3 resists neurotoxicity by increasing the expression of nerve growth factor[65]. Ginsenoside Rg1 has a neuroprotective effect, which is associated with decreased expression of aquporin (AQP4), which decreases the permeability of the blood-brain barrier and the degree of brain edema[66].

Improvement of impaired mitochondrial functions

The SARS-CoV-2 infection hijacks mitochondrial function and alters the host's metabolic pathways and immune responses to facilitate pathogenesis. Impairment of mitochondrial structure and function induces energy metabolism deficiency. When energy is depleted, fatigue and exhaustion sensations occur in patients with LC[67]. Lactate dehydrogenase (LDH) is a crucial enzyme in energy metabolism that catalyzes the bidirectional conversion of lactate to pyruvate and NAD^+ to reduce NAD^+ (NADH). Thus, elevated LDH levels in COVID-19 not only indicate the struggle of an individual's body to generate energy, but also reflect mitochondrial dysfunction[68–69].

Animal studies have demonstrated that *Ginseng Radix et Rhizoma* exerts anti-fatigue effects by improving energy metabolism. In fatigue-related behavioral trials, panaxydol, an active component of wild *Ginseng Radix et Rhizoma*, enhanced forced swimming performance by changing the subject's LDH level[70]. Polysaccharides, such as mixed water-soluble polysaccharides, can reduce immobility periods by lowering LDH and creating phosphokinase activities[71]. 20(S)-protopanaxatriol can significantly extend both swimming time in forced swimming trials and running times in rotarod tests[72]. It can also significantly increase glucose levels while decreasing corticosterone, blood lactic acid, free fatty acid, and LDH activity[72]. Furthermore, in postoperative fatigue syndrome induced by major small intestinal resection rat models, ginsenoside Rb1 not only increased maximum grip strength but also reversed enhanced BLA and LDH activity[73].

Ginseng Radix et Rhizoma-based formulas for LC treatment

The variation in SARS-CoV-2 and the complicated progression of LC indicate that single drugs alone may be modest and hampered by resistances or side effects in clinical settings. Therefore, holistic therapies based on compound prescriptions often achieve a better curative efficacy and fewer side effects. Such recipes have not only been practiced in traditional Chinese medicine as formulas for thousands of years, but are also increasingly accepted and becoming popular in modern medicine[74]. Notably, reasonable compatibility plays a significant role in the valuable formula, which is not a simple quantitative addition of herbs, but generates the outcome of synergism and attenuation[75].

As the most common symptom in LC, profound fatigue is a challenge for both patients and healthcare providers. Since sparse clinical practice and various animal-based experiments have already confirmed the safe anti-fatigue effects of *Ginseng Radix et Rhizoma*, as well as its components, *Ginseng Radix et Rhizoma* is currently prescribed in the formula for LC clinical treatment (Table 2). Notably, most of these employ *Ginseng Radix et Rhizoma* as "Monarch", which is the main efficacy-contributing herb in the formula. Among these formulas, it is noteworthy that Qingjin Yiqi granules significantly alleviate fatigue and have been recommended by the *Rehabilitation Guidelines of Integrated Medicine* for LC treatment in clinics[76].

Table 2

Formulas based on *Ginseng Radix et Rhizoma* in COVID-19 treatment.

Indication	Formula	Component
Qi deficiency	Qingjin Yiqi granule	*Ginseng Radix et Rhizoma, Ophiopogonis Radix, SchisandraeChinensis Fructus, Poria, Pinelliae Rhizoma, Scrophulariae Rhizoma, Atractylodis Rhizoma, Citri Reticulatae Pericarpium, Glycyrrhizae Radix et Rhizoma, Bupleuri Radix, Cimicifugae Rhizoma, Coicis Semen, Scutellariae Radix, Verbenae Herba, Phragmitis Rhizoma, Lophatheri Herba*
	Bufei decoction	*Ginseng Radix et Rhizoma, Astragali Radix, Rehmanniae Radix Preparata, Schisandrae Chinensis Fructus, Asteris Radix et Rhizoma, Mori Cortex*
	Baoyuan decoction	*Ginseng Radix et Rhizoma, Astragali Radix, Glycyrrhizae Radix et Rhizoma, Cinnamomi Cortex*
	Dabuyuan decoction	*Ginseng Radix et Rhizoma, Dioscoreae Rhizoma, Rehmanniae Radix Preparata, Eucommiae Cortex, Angelicae Sinensis Radix, Corni Fructus, Lycii Fructus, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle*
	Renshen Yangrong decoction	*Astragali Radix, Angelicae Sinensis Radix, Cinnamomi Cortex, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Citri Reticulatae Pericarpium, Atractylodis Macrocephalae Rhizoma, Ginseng Radix et Rhizoma, Paeoniae Radix Alba, Rehmanniae Radix Preparata, Schisandrae Chinensis Fructus, Poria, Polygalae Radix, Zingiberis Rhizoma Recens, Jujubae Fructus*
Blood stasis	Xiaochaihu decoction	*Bupleuri Radix, Pinelliae Rhizoma, Ginseng Radix et Rhizoma, Glycyrrhizae Radix et Rhizoma, Scutellariae Radix, Zingiberis Rhizoma Recens, Jujubae Fructus*

Concluding remarks and future perspectives

After SARS-CoV-2 infection, sustained fatigue in LC shares features with ME/CFS, which can be caused by chronic inflammation, over-activation or weakening of the immune system, autonomic dysfunction, malfunction in the hypothalamic-pituitary-adrenal axis, and neuroendocrine dysregulation. Compelling evidence has shown that *Ginseng Radix et Rhizoma* has anti-viral activity in both clinical and animal studies. In animal models, *Ginseng Radix et Rhizoma* bioactive components—including ginsenosides, polysaccharides, and volatile oils—have been reported to exert immune regulatory functions to reduce the release of pro-inflammatory and inflammatory cytokines. *In vivo* studies, both in animal models and in clinical practice, have reported that bioactive components of *Ginseng Radix et Rhizoma* improve mitochondria-mediated energy production and regulate the endocrine system. These findings suggest that *Ginseng Radix et Rhizoma* is a promising therapeutic agent for treating LC-related fatigue. Some *Ginseng Radix et Rhizoma*-based formulas have been developed to maximize its curative efficacy while minimizing any side effects. Medical herbs, such as *Ginseng Radix et Rhizoma*, usually contain complex compound repertoires with functionally diverse roles that form a sophisticated network. Although positive clinical outcomes of *Ginseng Radix et Rhizoma* against fatigue have been shown, further investigations and quantitative analyses are required to understand the underlying cellular and molecular mechanisms and the responsible bioactive compounds. This outcome will inspire new strategies for personalized medicine formulas according to the condition of individual patients with optimized efficacy.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Yu Wang and Yanyan Wang conceived and designed the review; Xiangda Zhou and Keying Zhang drafted this article; and Yu Wang, Yanyan Wang, Bin Qu, Rui Shao, Qianru Zhao, Lanbo Liu, and Ming Huang revised the manuscript. All the authors have read and approved the final manuscript.

Ethical approval of studies and informed consent

Not applicable

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